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Intermolecular [2 + 2] Cycloaddition of 1,4-Dihydropyridines with Olefins via Energy Transfer

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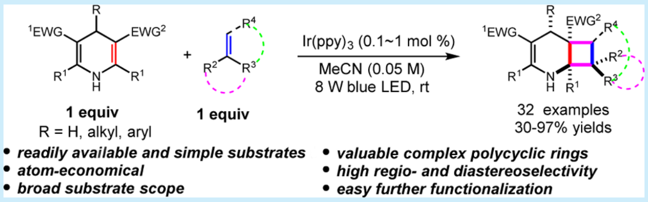
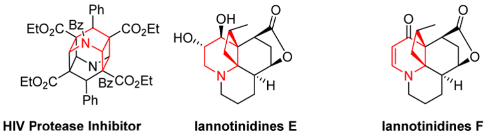
Supporting Information

ABSTRACT: A highly regio- and diastereoselective visible-light-promoted [2 + 2] cycloaddition between readily available 1,4-dihydropyridines and olefins has been developed. This strategy is operationally simple and atom-economical and enables the construction of strained polysubstituted 2-azabicyclo[4.2.0]octanes with three all-carbon quaternary centers with good functional group tolerance. These products can be easily converted to various structurally unique derivatives. The primary mechanistic studies demonstrated that the reaction proceeds through an energy transfer pathway.



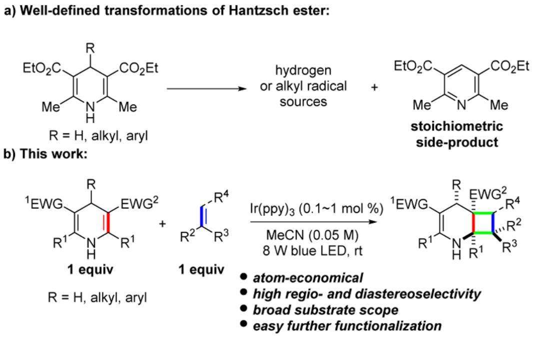
Strained polycyclic scaffolds containing cyclobutane rings are common motifs in many natural and artificial products (Scheme 1) that have extensively been used in organic synthesis, materials science, and biochemistry.[1] The photo-induced [2 + 2] cycloaddition reaction of olefins[2] is one of the ideal and straightforward methods to obtain multisubstituted cyclobutanes. Generally, complex intramolecular dienes or superstoichimetric amounts of olefins have to be used to guarantee the efficiency of [2 + 2] cycloaddition reactions. Thus, the development of highly efficient, selective, and atom-economical strategies for the preparation of strained polycyclic scaffolds from simple starting materials is continuously desirable. Additionally, it will be ideal that the obtained polycycles can easily undergo various derivatizations.

Scheme 1. Cyclobutane-Containing Alkaloids or Bioactive Structures



Hantzsch ester (1,4-dihydropyridine, 1,4-DHP) as a synthetic NADH analogue has been proven to be an efficient hydrogen donor[3] or alkyl radical source[4] in various useful transformations. However, these processes provide stoichiometric substituted pyridines as side products (Scheme 2a). The [2 + 2] photocycloaddition reactions of 1,4-DHPs with olefins could potentially afford polysubstituted strained 2-azabicyclo[4.2.0]octanes. The Adembri group reported an intermolecular [2 + 2] cycloadddition of *N*-benzyl-1,4-dihydronicotinamide with acrylonitrile under irradiation with a low-pressure mercury lamp that resulted in a 2:3 *cis*/*trans* product ratio.[5] The reaction has shown some drawbacks such as the use of a high-energy light source, dimerization of the starting material, and formation of product mixtures with poor regio- and stereoselectivities. To the best of our knowledge, highly regio- and diastereoselective [2 + 2] cycloaddition reactions of 1,4-DHPs with olefins have not been reported to date. Herein we present an efficient visible-light-promoted [2 + 2] cycloaddition of readily available 1,4-DHPs and olefins with high regio- and diastereoselectivities to construct polysubstituted, strained 2-azabicyclo[4.2.0]octanes (Scheme 2b).

Scheme 2. Useful Transformations of 1,4-Dihydropyridines



At the beginning of our studies, readily available Hantzsch ester (**1a**) and simple styrene (**2a**) were chosen as model substrates. In the presence of Ir(ppy)$_3$ (2 mol %) as the photocatalyst, the reaction of **1a** and **2a** (1 equiv) was carried out in a solution of MeCN (0.05 M) under irradiation with an 8 W blue LED and an atmosphere of nitrogen at room temperature (Table 1, entry 1). Two cyclobutanes, **3a** and **3a′**, were isolated in 77% combined yield, as confirmed by X-ray diffraction,[6] which showed that the reaction underwent a head-to-head pathway with a 3:1 *exo*/*endo* ratio. When a phenyl group was introduced at the 4-position of the 1,4-DHP (**1b**),

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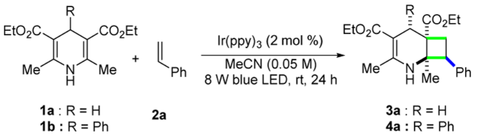
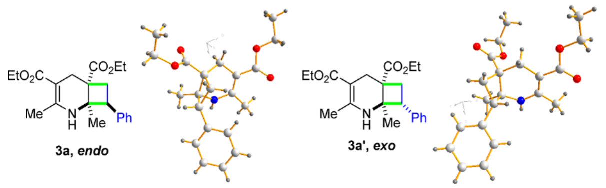
Table 1. Reaction Optimization[a]



entry	R	changes	yield of 4a (%)[b]
1	H (**1a**)	–	77 (**3a**[c])
2	Ph (**1b**)	–	65
3	Ph (**1b**)	without light	0
4	Ph (**1b**)	without Ir(ppy)$_3$	0
5	Ph (**1b**)	with air	0
6	Ph (**1b**)	THF	63
7	Ph (**1b**)	DMF	55
8	Ph (**1b**)	DMSO	42
9	Ph (**1b**)	CH$_2$Cl$_2$	39
10	Ph (**1b**)	acetone	54
11	Ph (**1b**)	with Et$_3$N (1 equiv)	55
12	Ph (**1b**)	with K$_2$CO$_3$ (1 equiv)	53
13	Ph (**1b**)	with water (10 equiv)	57
14	Ph (**1b**)	with AcOH (1 equiv)	55
15[d]	Ph (**1b**)	48 h	78

[a] Conditions: **1** (1 equiv), olefin (1 equiv), Ir(ppy)$_3$ (2 mol %), MeCN (0.05 M), 8 W blue LED, rt, 24 h. [b] Determined by ^{1}H NMR analysis using TMSPh as an internal standard. [c] The *endo*/*exo* ratio was 1:3.

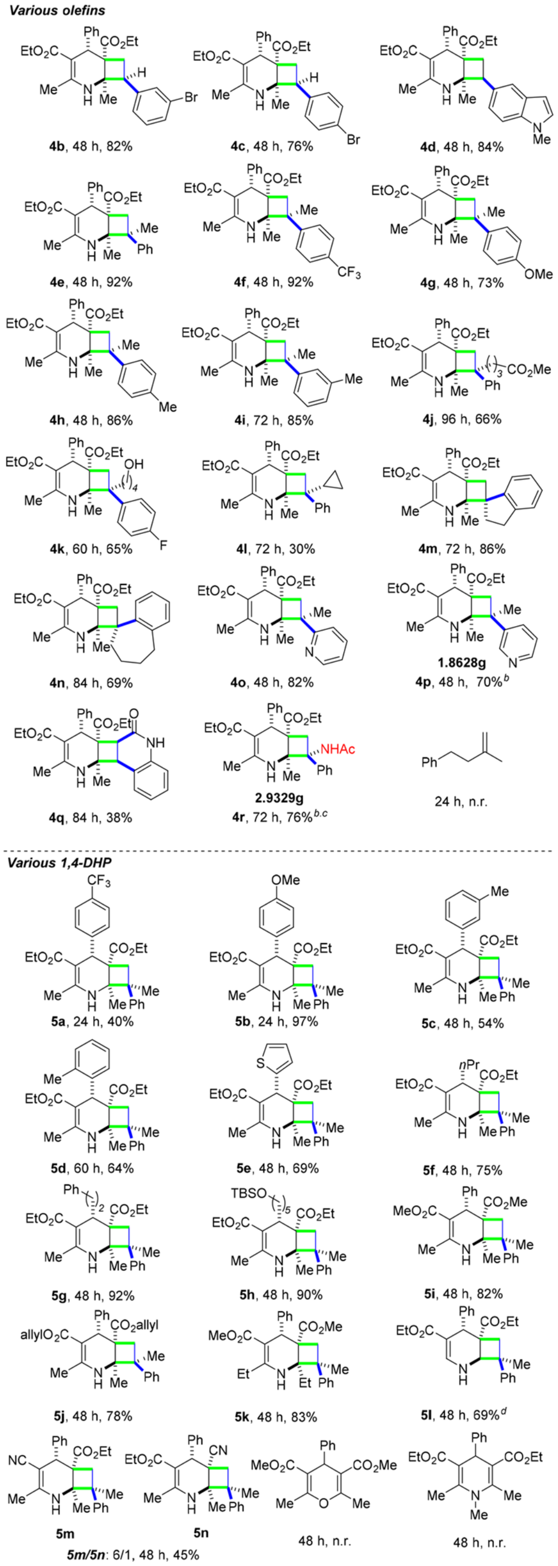


[d] Ir(ppy)$_3$ (1 mol %).

the reaction of **1b** with **2a** afforded **4a**[7] in 65% yield with high regio- and diastereoselectivities (entry 2). The diastereoconfiguration was confirmed by X-ray diffraction, which showed that the phenyl group of the styrene was seated proximal to the 1,4-DHP scaffold as a result of steric hindrance of the phenyl group on the 1,4-DHP scaffold. Control experiments indicated that both light and the photocatalyst were necessary (entries 3 and 4). No desired product was detected under exposure to air (entry 5). Various solvents such as THF, DMF, DMSO, CH$_2$Cl$_2$, and acetone were suitable for this reaction but afforded **4a** in slightly lower yields (entries 6−10). The reactions with an organic base (Et$_3$N) or an inorganic base (K$_2$CO$_3$) proceeded smoothly to afford **4a** in 55% and 53% yield, respectively (entries 11 and 12). Notably, in the presence of water (10 equiv) or AcOH (1 equiv), no significant changes were observed (entries 13 and 14). The reaction using 1 mol % Ir(ppy)$_3$ for 48 h afforded **4a** in 78% yield (entry 15). Besides, the reaction exhibited good biocompatibility (Table S1 in the Supporting Information). The standard conditions were identified as follows: 1,4-DHP (1 equiv), olefin (1 equiv), and Ir(ppy)$_3$ (1 mol %) in MeCN solution (0.05 M) under irradiation with an 8 W blue LED at room temperature.

With the established reaction conditions, the scope of olefins was explored (Scheme 3). The diastereomeric ratios of all reactions were greater than 10:1 unless otherwise noted. With 3- or 4-bromostyrenes as olefin partners, which were easily further derivatized, the reactions were carried out smoothly to afford the corresponding cyclobutanes **4b** and **4c** in 76% and 82% yield, respectively. Indole-containing 2-azabicyclo[4.2.0]octane **4d** was obtained in 84% yield with *N*-methyl-5-

Scheme 3. Substrate Scope[a]



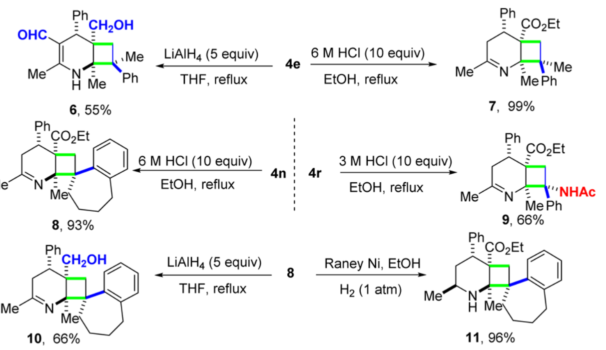
[a] Standard conditions: **1** (1 equiv), olefin (1 equiv), Ir(ppy)$_3$ (1 mol %), MeCN (0.05 M), 8 W blue LED, rt. [b] The gram-scale reaction was performed using 0.1 mol % Ir(ppy)$_3$ in MeCN (0.10 M). [c] Isolated by direct filtration from the reaction mixture without further purification. [d] *endo*/*exo* = 6:1.

vinylindole as an alkene partner. α-Methylsytrenes with both electron-donating and withdrawing groups were suitable for this catalytic reaction, giving **4e**−**g** in 72−92% yield. Additionally, long alkyl chains with ester and free alcohol at the α-position of the styrene were tolerated, delivering **4j** and **4k** in 65−66% yield. Furthermore, sterically hindered α-cyclopropylstyrene could also participate in the cycloaddition for a long time to afford **4l** in 30% yield without any ring-opening products. Remarkably, structurally rare spiro[3.4]octane **4m** and spiro[3.6]decane **4n**[8] can be accessed via this strategy in 69−86% yield with high regio- and stereoselectivities. Interestingly, quinolin-2(1*H*)-one can also participate to afford **4q** in 38% yield, which illustrates that this method could potentially be used as a late-stage functionalization strategy. The non-phenyl pyridyl group could also be employed in this reaction to deliver **4o** in 82% yield. With 0.1 mol % Ir(ppy)$_3$, the reaction can easily be scaled up to afford pyridine-containing cyclobutane **4p** in 70% yield (1.86 g) and acetylamide-substituted cyclobutane **4r** in 76% yield (2.93 g). Notably, **4r** could be directly obtained by filtration from the reaction mixture without further purification. So far, aliphatic alkenes were not suitable in this transformation.

Then the substituents on the 1,4-DHPs were investigated. The reaction of 4-(4′-trifluoromethyl)phenyl dihydropyridine provided the desired cyclobutane **5a** in 40% yield and overoxidized pyridine as a side product in 54% yield. Electron-rich 4-(4′-methoxy)phenyl dihydropyridine was converted to **5b** in 97% yield. The 3-methylphenyl and more sterically hindered 2-methylphenyl groups at the 4-position of the dihydropyridine were tolerated (**5c** and **5d**). A heteroaryl ring (2-thiophenyl) was suitable, affording **5e** in 69% yield. It should be noted that aliphatic 1,4-DHPs participated to give **5f**−**h** in 75−92% yield. Dihydropyridines with various substituents on the ester group or 2- and 6-positions reacted under standard conditions to give **5i**−**k** in 78−83% yield. The reaction of a less sterically demanding dihydropyridine without substituents at the 2- and 6-positions afforded **5l** in 69% yield with 6:1 dr. The unsymmetrical mono-CN substrate could be reacted to deliver a mixture of **5m** and **5n** in 45% yield with a ratio of 6:1. When oxygen instead of nitrogen on the 1,4-DHP or *N*-methyl-protected 1,4-DHP was used, the reaction did not occur.

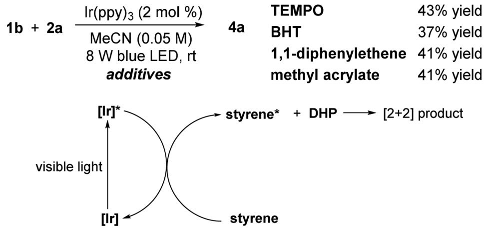
With regard to the synthetic utility, various derivatizations were conducted (Scheme 4). Simple treatment of **4e** with LiAlH$_4$ delivered a 55% yield of the unique and selective reduction product **6**, in which one ester group was reduced to the alcohol while the other was reduced to the aldehyde. The de-esterification reactions of **4e**, **4n**, and **4r** could be performed by refluxing in a solution of ethanol with aqueous HCl to afford the corresponding products in 99% (**7**), 93% (**8**), and 66% (**9**) yield, respectively. The rare spiro[3.6]decane **8** could be selectively reduced using LiAlH$_4$ to afford ester reduction product **10** in 66% yield and using Raney Ni with H$_2$ to afford imine reduction product **11** in 96% yield.

Scheme 4. Further Derivatization



To provide some insights into the mechanism of this reaction, control experiments in the presence of various radical trappers (1 equiv), such as TEMPO, BHT, 1,1-diphenylethene, and methyl acrylate, were carried out to afford cyclobutane **3** in a slightly lower yield (Scheme 5). Additionally, the reaction could tolerate various solvents and acidic and basic conditions (Table S1). On the basis of redox potential, neither Ph-DHP **1b** ($E_{1/2}^{\text{red}}$ = +0.85 V vs SCE)[9] nor styrene ($E_{1/2}^{\text{red}}$ = +1.88 V vs SCE)[10] could be oxidized by the photoexcited species Ir(ppy)$_3$* ($E_{1/2}^{*\text{III/II}}$ = +0.31 V vs SCE).[11] These experiments indicated that a redox radical-initiated cycloaddition pathway was less possible. The triplet energies of 4-substituted Hantzsch esters,[12] styrenes,[13] and ^{3}Ir(ppy)$_3$* were around 68, 62 and 59 kcal/mol.[14] These data were quite similar, which demonstrated that the reaction could proceed via an energy transfer pathway. A proposed mechanism is shown in Scheme 5. The photosensitizer Ir(ppy)$_3$ absorbs visible light to generate the excited state Ir(ppy)$_3$*, which undergoes energy transfer to styrene to afford excited state styrene* and regenerate Ir(ppy)$_3$. Then styrene* can be trapped by the Hantzsch ester to afford to the corresponding [2 + 2] cycloaddition product.

Scheme 5. Radical Trapping Experiments and Proposed Mechanism



In summary, we have developed a novel regio- and diastereoselective visible-light-promoted [2 + 2] cycloaddition of 1,4-DHPs and olefins. This protocol is operationally simple and atom-economical and uses relatively simple and readily available starting materials for the efficient synthesis of more valuable polysubstituted 2-azabicyclo[4.2.0]octanes. Various derivatizations could be realized for the construction of structurally unique azabicycles or spiro rings. The primary studies demonstrated that the reaction proceeds via an energy transfer pathway. The protocol has also demonstrated great biocompatibility and could potentially be used in biochemistry. The photocatalytic synthesis of valuable complex molecules is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02881.

Experimental details, characterization data for all compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data for **3a** (CIF)

Crystallographic data for **3a′** (CIF)
Crystallographic data for **4a** (CIF)
Crystallographic data for **4n** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *The Chemistry of Cyclobutanes*; Rappoport, Z., Liebman, J. F., Eds.; John Wiley & Sons: Chichester, U.K., 2005. (b) Sergeiko, A.; Poroikov, V. V.; Hanuš, L. O.; Dembitsky, V. M. *Open Med. Chem. J.* **2008**, *2*, 26. (c) Dembitsky, V. M. *J. Nat. Med.* **2008**, *62*, 1. (d) Hong, Y. J.; Tantillo, D. J. *Chem. Soc. Rev.* **2014**, *43*, 5042. (e) Dembitsky, V. M. *Phytomedicine* **2014**, *21*, 1559. For cyclobutanes in catalysis, see: (f) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740; *Angew. Chem.* **2011**, *123*, 7884. For cyclobutanes in materials science, see: (g) Han, Y.; Jin, G. *Acc. Chem. Res.* **2014**, *47*, 3571. (h) Sinha, N.; Hahn, F. E. *Acc. Chem. Res.* **2017**, *50*, 2167.

(2) For reviews of [2 + 2] photocycloaddition, see: (a) Hehn, J. P.; Müller, C.; Bach, T. Formation of a Four Membered Ring: From a Carbonyl-Conjugated Alkene. In *Handbook of Synthetic Photochemistry*; Albini, A., Fagnoni, M., Eds. Wiley-VCH: Weinheim, Germany, 2010; p 171. (b) Margaretha, P. *Helv. Chim. Acta* **2014**, *97*, 1027. (c) Poplata, S.; Tröster, A.; Zou, Y.; Bach, T. *Chem. Rev.* **2016**, *116*, 9748. (d) Yoon, T. P. *Acc. Chem. Res.* **2016**, *49*, 2307. For selected recent examples of intramolecular [2 + 2] photocycloaddition with olefins, see: (e) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572. (f) Austin, K. A. B.; Herdtweck, E.; Bach, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8416. (g) Brimioulle, R.; Bach, T. *Science* **2013**, *342*, 840. (h) Vallavoju, N.; Selvakumar, S.; Jockusch, S.; Sibi, M. P.; Sivaguru, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5604. (i) Brimioulle, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.* **2015**, *137*, 5170. (j) Huang, X.; Quinn, T. R.; Harms, K.; Webster, R. D.; Zhang, L.; Wiest, O.; Meggers, E. *J. Am. Chem. Soc.* **2017**, *139*, 9120. For selected recent examples of intermolecular [2 + 2] photocycloaddition with olefins, see: (k) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (l) Coote, S. C.; Bach, T. *J. Am. Chem. Soc.* **2013**, *135*, 14948. (m) Hurtley, A. E.; Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 8991. (n) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392. (o) Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. *Science* **2016**, *354*, 1391. (p) Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.* **2016**, *138*, 7808. (q) Zhao, J.; Brosmer, J. L.; Tang, Q.; Yang, Z.; Houk, K. N.; Diaconescu, P. L.; Kwon, O. *J. Am. Chem. Soc.* **2017**, *139*, 9807.

(3) For selected reviews of Hantsch ester as a hydrogen donor, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (c) Zheng, C.; You, S. *Chem. Soc. Rev.* **2012**, *41*, 2498. (d) Huang, W.; Cheng, X. *Synlett* **2017**, *28*, 148.

(4) (a) Li, G.; Chen, R.; Wu, L.; Fu, Q.; Zhang, X.; Tang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 8432. (b) Chen, W.; Liu, Z.; Tian, J.; Li, J.; Ma, J.; Cheng, X.; Li, G. *J. Am. Chem. Soc.* **2016**, *138*, 12312. (c) Nakajima, K.; Nojima, S.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 14106. (d) Gutiérrez-Bonet, Á.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. *ACS Catal.* **2016**, *6*, 8004.

(5) (a) Adembri, G.; Donati, D.; Fusi, S.; Ponticelli, F. *Heterocycles* **1985**, *23*, 2885. (b) Adembri, G.; Donati, D.; Fusi, S.; Ponticelli, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2033. For a dimerization, see: (c) Adembri, G.; Camparini, A.; Donati, D.; Fusi, S.; Ponticelli, F.; Scotton, M. *Tetrahedron Lett.* **1983**, *24*, 5399.

(6) CCDC number for **3a′**: 1526041. CCDC number for **3a**: 1526039.

(7) CCDC number for **4a**: 1526043.

(8) CCDC number for **4n**: 1565460.

(9) (a) Zapata-Urzúa, C.; Pérez-Ortiz, M.; Acosta, G. A.; Mendoza, J.; Yedra, L.; Estradé, S.; Álvarez-Lueje, A.; Núñez-Vergara, L. J.; Albericio, F.; Lavilla, R.; Kogan, M. J. *J. Colloid Interface Sci.* **2015**, *453*, 260. (b) Salazar, R.; Navarrete-Encina, P. A.; Camargo, C.; Squella, J. A.; Núñez-Vergara, L. J. *J. Electrochem. Soc.* **2008**, *155*, P103.

(10) Park, J.; Lee, Y.; Ohkubo, K.; Nam, W.; Fukuzumi, S. *Inorg. Chem.* **2015**, *54*, 5806.

(11) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(12) Jimenez, A. J.; Fagnoni, M.; Mella, M.; Albini, A. *J. Org. Chem.* **2009**, *74*, 6615.

(13) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

(14) Noh, Y.; Lee, C.; Kim, J.; Yase, K. *J. Chem. Phys.* **2003**, *118*, 2853.